An efficient stimulus design for detecting neuronal non-linearities with BOLD fMRI

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Introduction

The m-sequence probe method (1-4) allows for efficient estimation of non-linear effects in fMRI (4). A binary m-sequence is a pseudo random sequence, whose bit values represent two stimulus conditions, one active and one rest state. Some properties of these sequences are: a) they can be easily generated with a shift register with appropriate feedback taps; b) their auto correlation is a delta function; c) the product of a sequence with a shifted version of itself results in the same sequence with a different shift. The second property makes m-sequences very useful for estimating the BOLD response curve, while the third property allows for determination of nonlinear characteristics of the response (1). Because the BOLD is slow, acts as a low-pass filter and is to a large extent linear (4), while the (mostly neuronal) nonlinear processes are fast, the standard m-sequence design does not have optimal sensitivity. This study presents a stimulus paradigm that has improved sensitivity compared to the standard m-sequence, while retaining other favorable m-sequence properties.

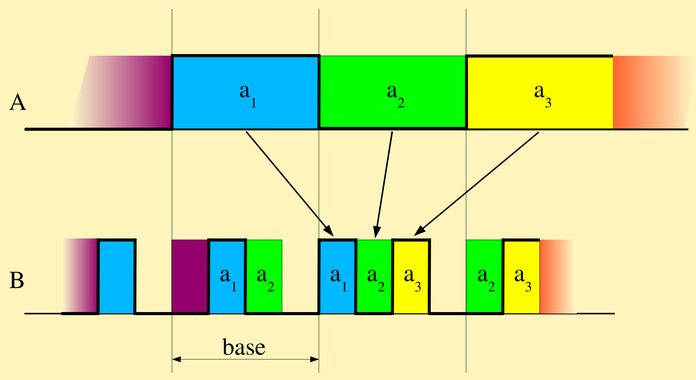

Figure 1.
Part of a standard m-sequence design (A) and the modified sequence derived from it (B) by reducing the bin-length and repeating the bins a number of times.

Theory

A m-sequence consists of 2^n-1 sequential bins (Fig. 1a), having a pseudo-random binary value. Each controls a stimulus condition; for example, when the sequence is one a checkerboard pattern is shown, when it is zero, a gray screen is presented. For stimulation of the fast nonlinear elements, the stimulus spectrum needs to have energy in the higher frequencies, i.e. for a large nonlinear neuronal response the binsize needs to be short, creating a high density of transitions in the stimulus. This because most non-linear effects are thought to be related to the detection of a contrast change and have a relatively short time constant. Reducing the binsize however spreads the power over a larger portion of the spectrum, leading to a low output of the BOLD signal because of its low-pass characteristics, suppressing rapidly changing signals.

A possible solution is to reduce the bin size, but at the same time repeat every bit of the sequence a couple of times, as shown in Fig. 1b. This leads to the desired high number of transitions, while the averaging effect of the repeated bits concentrates the power in the frequency band of the BOLD. Every second, a gap is inserted to prevent retrograde interactions (from a2 to a1 etc.).

A simulation shows the linear effects of the modified sequence are equivalent to a slow sequence, while the non-linear effects are amplified compared both to a slow and a fast standard m-sequence (Fig 2).

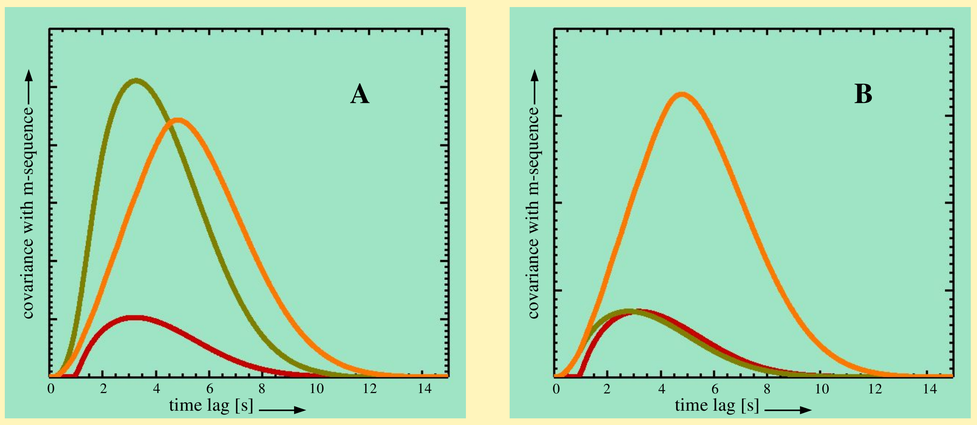

Figure 2.
Simulated response signals, measured as covariance with the m-sequence used, for linear (A) and non-linear (B) effects. The three lines indicate the response to a normal 1s binsize sequence in green, a 200ms binsize sequence in red, and a modified sequence with five repeated 200ms bins in orange A BOLD impulse response of about 5s width is assumed. The non-linear effects are assumed to be originating from the transitions in the contrast and to produce stimulation for about 100ms. The non-linear response of the modified m-sequence is stronger than the slow sequence because it has more transitions, and stronger than the fast sequences because a number of the transitions is averaged, effectively reducing the bandwidth of the stimulus.

Methods

The design was tested on six volunteers, scanned after giving informed consent under IRB approved protocol on a GE 3T scanner with a 16 channel Nova head coil and home build digitizer. Scan parameters: rate 2 SENSE EPI, TR 1s, TE 40ms, 192x144 pixels over 220x165mm field of view, 8 slices, thickness/gap= 1.5/0.5mm, 600 repetitions. A 255 bin m-sequence was used, extended to 300 bins by repeating the first 45 bins, and followed by it inverse. Each second contained 5 bits of 130ms, plus 350ms gap. The stimulus was circular checkerboard projected on a screen in the bore, with condition 1 being a single contrast reversal and condition 0 and the gaps a uniform gray field. The data was analyzed by taking the covariance of each pixel time course with the m-sequence in two sections of 255, from the first and second half of the scan. Repeating the sequence with it's inverse has the advantage that the linear terms are inverted in the response, but the (second order) non-linear terms are not, so the comparison between the first and second half can discriminate between them.

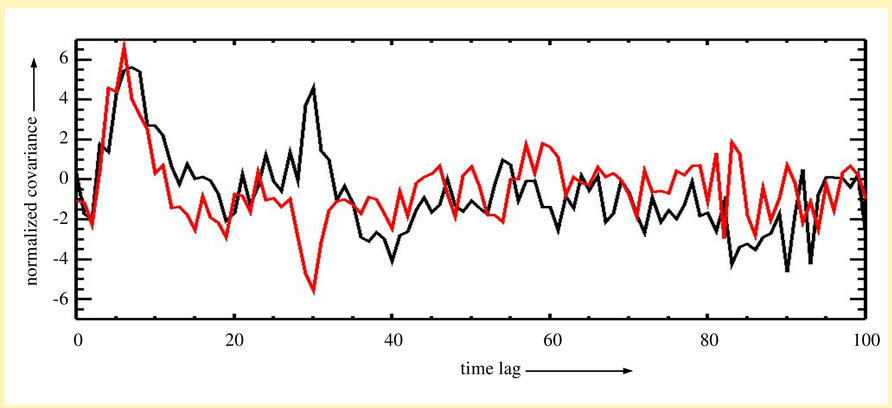

Figure 3.
Example of the correlation of single voxel data with the m-sequence. The black line is from the first half of the experiment, the red line from the second, which is the inverse repeat (correlated with the inverse sequence). As expected both linear peaks are positive, while the second order peak (at lag 30) is inverted.

Results & Discussion

All volunteers showed robust first order activation. The second order averaged 18% (range 0-45%) of the first order as measured in the active pixels in early visual areas. An example of the resulting correlation in a single pixel is plotted in Fig. 3, showing the first sequence (black) and the inverse repeat (red). The curves are normalized to the temporal SD in the correlogram. Maps of single time lags in the first and second order peaks of the correlogram are shown in Fig. 4, based the average of the first and second half of the experiment. Clearly observable is the second order response in the same area as the first order, although with lower amplitude. The main applications of this method are expected to be in the study of sensory systems.

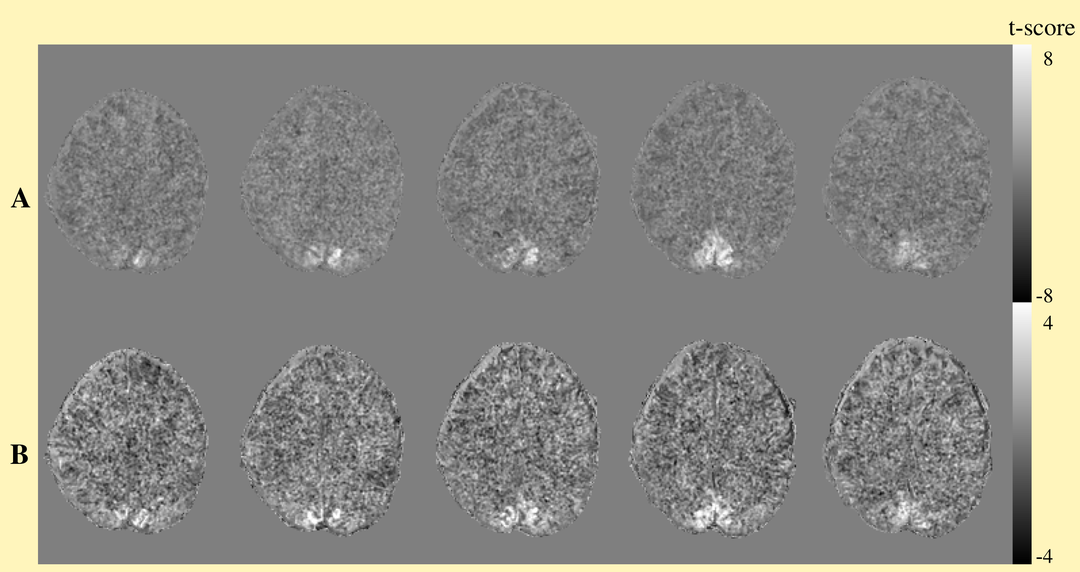

Figure 4.
Example of the covariance maps obtained with the modified m-sequence stimulus. Presented are five out of eight slices, showing one time lag of the covariance for the linear response in the top row (A) and the second order non-linear response on the bottom (row B). The maps are scaled to the noise, i.e. making it a t-score. The scaling is indicated on the right; the bottom row is scaled twice as bright as the top row.

References

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